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The purpose of the present study is to assess the potential drug etiology of breast cancer through analyses of data from our hospital-based Case-Control Surveillance Study. We carried out computer "screens" of the data to detect unsuspected associations: the use of each drug or drug class among women with breast cancer was compared to that among women admitted for other conditions. Odds ratios were significantly elevated or reduced for several drugs; these relationships will be assessed in detailed analyses. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated in several studies with a reduced risk of large bowel cancer. We assessed NSAID use in relation to breast cancer risk in comparisons of 6558 cases of breast cancer to 3296 cancer and 2925 noncancer controls. In the analysis using noncancer controls, the odds ratio was compatible with a small reduction in the risk of breast cancer among regular users of NSAIDs. However, the reduction was attributable to one study center that contributed less than 10% of the data. With cancer controls there was no reduction. The results, including analyses of the duration and timing of use, do not support an inverse association between NSAID use and the risk of breast cancer.

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Lyn Rosenbury Aug 28, 1997

PI - Signature Date

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INTRODUCTION

Several drugs have been involved in the etiology of cancer. For example, postmenopausal estrogen supplements are associated with an increased risk of endometrial cancer.[1] It is possible that drugs might be involved in the etiology of breast cancer as well. Oral contraceptive use[2] and postmenopausal female hormone use[3] have been assessed, but there has not been a systematic assessment of other drugs that might be associated with the risk of breast cancer. The purpose of the present study is to begin such a systematic assessment, through analyses of data from our Case-Control Surveillance Study of drugs and cancer.

In accord with our Statement of Work, we carried out computer "screens" of the data, in which the use of individual drugs or drug classes among women with breast cancer was compared to that among women who had been admitted for other conditions. The purpose of these comparisons was the detection of unsuspected associations. In addition, we carried out a detailed case-control analysis of the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in relation to breast cancer risk. A substantial body of evidence suggests that the use of NSAIDs reduces the risk of colon cancer.[4,5] By contrast, there have been relatively few studies of NSAID use in relation to breast cancer risk and findings have been inconsistent.[6-10] There is a need for further data.

BODY

Data. The data used were collected from 1976 through 1996 from patients less than 70 years of age, in hospitals in New York, Philadelphia, Baltimore, and Boston. Nurse-interviewers administered standard questionnaires to obtain information on demographic factors, reproductive and medical history, and habits such as alcohol consumption. Histories of drug use were elicited by questions about 42 indications, which included those for which NSAIDs are used (e.g., pain, headache, and arthritis). For each episode of use, the drug name and the duration, timing, and frequency of use were recorded. Details of the diagnoses were abstracted from discharge summaries and pathology reports. Of patients approached, 96% participated.

Computer screens

The drug use among women who had been diagnosed with breast cancer within the previous year (6957 women) was compared with that of 7262 women who had been admitted for other cancers. Unlike in the detailed analyses of NSAID use described below, women were not excluded if they were under 30 years of age or if they had a concurrent or previous cancer. For each drug or drug class in turn, odds ratios were computed for use relative to nonuse, with control for age and study center. Over 250 individual drugs and over 150 drug classes (e.g., beta adrenergic blockers, oral anticoagulants) were assessed. Similar analyses were conducted in which the breast cancer cases were compared with 30,223 women admitted for nonmalignant conditions.

In both the screen using cancer controls and the screen using noncancer controls, there were a number of statistically significant associations with drugs that have been previously

related to an increased risk of breast cancer, such as oral contraceptives. Among drugs which have not previously been assessed in relation to the risk of breast cancer, heparin use (67 case users) was associated with a decreased risk; oral anticoagulant use (173 case users) was associated inversely with risk as well, but the association was weaker. The odds ratio for cimetidine use (211 case users), which is used for the treatment of gastric ulcers, was also reduced. The odds ratio was increased for clomiphene citrate (76 case users), a fertility drug.

NSAID use and the risk of breast cancer

Cases and controls. The women included in these analyses were 30 through 69 years of age. The cases comprised 6558 women with a first occurrence of primary breast cancer diagnosed within the previous year, and no concurrent or previous cancer. Two control groups of patients with diagnoses judged to be unrelated to NSAID use were selected. A cancer control group comprised 3296 patients with ovarian or uterine cancer (49%), malignant melanoma (21%), respiratory system cancer (22%), or nervous system or endocrine cancer (8%). As with the cases, the control cancers had been diagnosed no more than one year previously, and there was also no history of another cancer. A noncancer control group included 2925 patients admitted for trauma (56%) or acute infection (44%), who had no history of cancer. The controls were frequency-matched to the cases on five-year age group, interview year, and study center.

Analysis. NSAID use was defined as use of any drug in the following classes: salicylates (e.g., aspirin), indoles (e.g., indomethacin), propionic acids (e.g., ibuprofen), fenamates (e.g., mefenamic acid), pyrazolines (e.g., phenylbutazone), and oxicams (e.g., piroxicam). Most use was sporadic. We judged that if NSAID use has a preventive role, it would most likely be regular use of long duration. We defined regular NSAID use as use of an NSAID at least four times per week for three or more months. All other use was considered nonregular. Regular use was further subdivided according to when NSAIDs were first and last used (within the previous year, or more than one year prior to interview). Only use that began a year or more before interview was considered to be etiologically relevant.

The prevalence of regular NSAID use that began at least one year before interview, adjusted for study center and five-year age group, was 7.3% among cancer controls and 9.2% among noncancer controls. The prevalence varied by year of interview (higher in later years), geographic area (highest in Philadelphia and lowest in New York), and age (higher at older ages). Use was also positively associated with years of education, benign breast disease, number of doctor visits two years prior to hospitalization, and use of hormone supplements and oral contraceptives. Potential confounding by all these factors was controlled in the analysis: in unconditional logistic regression models used to estimate the odds ratios for regular NSAID use relative to never use, terms were included for age (five-year age group), study center, year of interview (1976-1980, 1981-1985, 1986-1990, 1991-1996), years of education (<12, 12, 13-15, 16+, missing), benign breast disease (yes, no, missing), number of doctor visits two years before hospitalization (0-2, 3-6, 7+, missing), duration of female hormone use (<5 years, 5+years, missing), and duration of oral contraceptive use (0, 1-4 years, 5+ years, missing). Terms were not included for variables which had little effect on the estimates: age at menarche, age at menopause, age at first birth, parity, race, alcohol consumption, religion, breast cancer in mother

or sister, practice of breast self examination, and body mass index. A continuous term was used to test for trend across duration of regular NSAID use among users.

Results. Data on nonregular and regular use of NSAIDs among the cases and controls are given in Table 1. For nonregular NSAID use the odds ratio was 0.9 (95% confidence interval (CI) 0.8-1.0) with cancer controls and 1.0 (95% CI 0.9-1.1) with noncancer controls. The odds ratio for use that began in the year before admission was 0.6 (0.4-1.0) using cancer controls and 0.5 (0.3-0.8) using noncancer controls. For subjects who used NSAIDs regularly beginning at least one year before admission, the odds ratio was 0.8 (95% CI 0.7-1.0) using cancer controls, and 0.7 (95% CI 0.6-0.9) using noncancer controls. When we limited the noncancer control group exclusively to subjects admitted for fractures, the odds ratio was 0.9 (95% CI 0.7-1.1). Regular NSAID use that continued into the year before interview (continuing use) was evaluated separately from use that was discontinued one or more years prior to interview (discontinued use). Using cancer controls, the odds ratio was 0.7 (95% CI 0.5-1.0) for discontinued use and 0.9 (95% CI 0.7-1.1) for continuing use. Using noncancer controls, the odds ratio was 0.9 (95% CI 0.7,1.4) for discontinued use and 0.7 (95% CI 0.6-0.8) for continuing use. The results obtained with the cancer controls were unchanged when cancers of the female genital tract (ovary and uterus) were excluded. All further analyses are confined to regular NSAID use that was begun at least a year before admission.

Odds ratios according to duration of regular NSAID use are given in Table 2. Using cancer controls, the odds ratio did not decrease as duration of regular use increased (p for trend = 0.98). Using noncancer controls the odds ratio decreased from 0.9 (95% 0.5-1.7) for less than one year of use to 0.6 (95% CI 0.3, 1.0) for 20 or more years of use, and the trend was significant (p = 0.01).

As shown in Table 3, the reduction in the odds ratio for regular NSAID use was apparent only in the earliest years of the study (1976 to 1980) (odds ratio (OR) = 0.5, 95% CI 0.3-0.7 using noncancer controls, and 0.7, 95% CI 0.4-1.0 using cancer controls), and in Boston (OR = 0.4, 95% CI 0.2-0.6 using noncancer controls and 0.5, 95% CI 0.3-1.0 using cancer controls). The reduction in risk for regular NSAID use that began at least a year before admission shown in Table 1 was largely accounted for by the reduced risk in the Boston center, which contributed 608 (9%) of the cases. When Boston patients were excluded, the odds ratio for regular NSAID use was 0.9 (95% CI 0.7-1.0) with cancer controls and 0.9 (95% CI .0.7-1.1) with noncancer controls (Table 4). With Boston excluded, the reduction in risk as duration of use increased, using noncancer controls, was attenuated (p for trend = 0.06) (Table 4).

Table 1. NSAID use in cases, cancer controls, and noncancer controls

NSAID use	Cases	Cancer controls	OR* (95% CI)	Noncancer controls	OR* (95% CI)
Never	1942	1089	1.0	1042	1.0
Nonregular	4086	1873	0.9 (0.8-1.0)	1565	1.0 (0.9-1.1)
Within 1 year of admission only	68	48	0.6 (0.4-1.0)	54	0.5 (0.3-0.8)
Regular use begun ≥1 year before admission	443	269	0.8 (0.7-1.0)	252	0.7 (0.6-0.9)
Discontinued use	109	68	0.7 (0.5-1.0)	54	0.9 (0.7-1.4)
Continuing use	334	201	0.9 (0.7-1.1)	198	0.7 (0.6-0.8)
Unknown	19	17	0.5 (0.2-1.0)	12	0.4 (0.2-1.0)

*Adjusted for age, study center, interview year, years of education, history of benign breast disease, number of doctor visits two years before admission, duration of use of oral contraceptives, duration of use of female hormone supplements.

Table 2. Regular NSAID use that began ≥1 year before admission, by duration

Duration	Cases	Cancer controls	OR* (95% CI)	Noncancer controls	OR* (95% CI)
Never	1942	1089	1.0	1042	1.0
Regular use begun ≥1 year before admission					
<1 year	39	20	0.8 (0.4-1.4)	21	0.9 (0.5-1.7)
1-<2 years	98	51	0.9 (0.7-1.4)	36	1.1 (0.7-1.7)
2-<5 years	125	87	0.7 (0.5-1.0)	75	0.7 (0.5-1.0)
5-<10 years	71	41	0.9 (0.6-1.3)	44	0.7 (0.4-1.0)
10-<20 years	61	37	0.9 (0.6-1.4)	37	0.7 (0.4-1.1)
20+ years	29	18	0.9 (0.5-1.7)	22	0.6 (0.3-1.0)
Unknown	39	32	0.5 (0.3-0.9)	29	0.4 (0.2-0.7)
P for trend			0.98		0.01

*Adjusted for age, study center, interview year, years of education, history of benign breast disease, number of doctor visits two years before admission, duration of use of oral contraceptives, duration of use of female hormone supplements.

Table 3. Regular NSAID use that began ≥1 year before admission, by interview year and study center

Subgroup	Cases	Cancer controls	OR* (95% CI)	Noncancer controls	OR* (95% CI)
1976-1980	65	58	0.7 (0.4-1.0)	87	0.5 (0.3-0.7)
1981-1985	181	102	0.8 (0.6-1.1)	52	1.0 (0.7-1.5)
1986-1990	76	43	1.4 (0.9-2.2)	48	1.0 (0.6-1.5)
1991-1996	121	66	0.8 (0.6-1.2)	65	0.9 (0.6-1.4)
Boston	28	33	0.5 (0.3-1.0)	81	0.4 (0.2-0.6)
New York	185	67	0.9 (0.6-1.2)	47	1.0 (0.7-1.5)
Philadelphia	200	123	1.0 (0.8-1.3)	110	0.8 (0.6-1.1)
Baltimore	30	46	0.6 (0.3-1.0)	14	1.1 (0.5-2.3)

*Adjusted for age, study center, interview year, years of education, history of benign breast disease, number of doctor visits two years before admission, duration of use of oral contraceptives, duration of use of female hormone supplements.

Table 4. NSAID use in cases, cancer controls, and noncancer controls, excluding Boston

NSAID use	Cases	Cancer controls	OR* (95% CI)	Noncancer controls	OR* (95% CI)
Never	1743	964	1.0	803	1.0
Nonregular	3716	1580	1.0 (0.9-1.1)	1139	1.0 (0.9-1.2)
Within 1 year of admission only	59	41	0.6 (0.4-1.0)	45	0.4 (0.3-0.7)
Regular use begun ≥1 year before admission	415	236	0.9 (0.7-1.0)	171	0.9 (0.7-1.1)
<1 year	36	17	0.9 (0.5-1.6)	13	1.1 (0.5-2.1)
1-<2 years	93	47	1.0 (0.7-1.4)	24	1.4 (0.9-2.3)
2-<5 years	117	76	0.8 (0.5-1.0)	57	0.7 (0.5-1.0)
5-<10 years	66	35	0.9 (0.6-1.5)	29	0.8 (0.5-1.3)
10-<20 years	57	33	0.9 (0.6-1.5)	26	0.8 (0.5-1.3)
20+ years	28	18	0.9 (0.5-1.7)	15	0.7 (0.4-1.4)
Unknown	35	24	0.6 (0.4-1.1)	14	0.6 (0.3-1.2)
P for trend			0.89		0.06

*Adjusted for age, study center, interview year, years of education, history of benign breast disease, number of doctor visits two years before admission, duration of use of oral contraceptives, duration of use of female hormone supplements.

CONCLUSIONS

Computer screens

Several associations, both positive and inverse, were observed in the computer screens of the data. As proposed in our grant proposal and our Statement of Work, if relevant medical, epidemiologic and toxicologic literature suggest that an association may have a plausible biologic basis, in the coming year we will carry out data analyses to assess the association in detail. The analyses will involve careful definition of the case and control series and control of confounding through multivariate analysis. We have had considerable experience in assessing unsuspected associations, and we are well aware that they may be chance findings. Only further data collection can address that possibility. Thus, any results published based on screen findings will be presented conservatively.

NSAID use and the risk of breast cancer

The present data do not provide persuasive support for a protective effect of NSAIDs against breast cancer. A small reduction in the odds ratio observed in the overall data for regular NSAID use that began at least a year before admission was accounted for by one study center, Boston, that contributed a relatively small amount of data, and there was no clear evidence of a risk reduction for quite long durations of use. With Boston included, a reduction in the odds ratio was more pronounced using noncancer controls, as was a reduction in risk as duration of use increased. With Boston excluded, the odds ratios for regular use begun at least one year before admission approached the null, whether cancer or noncancer controls were used; in addition, the trend according to the duration of use observed with noncancer controls was weakened. We can offer no explanation for the findings in Boston other and that the results were based on relatively small numbers (28 exposed cases) and could be due to chance.

With regard to the noncancer controls, we judged that trauma and acute infections were diagnoses for which hospital admission was largely obligatory. However, when we limited the noncancer controls to one group for whom admission was absolutely obligatory--fractures--the odds ratio approached the null. While there may have been selection bias in the present study, we believe it was not major, because there was no risk reduction for nonregular NSAID use using either cancer or noncancer controls.

In our analysis of colon cancer and NSAID use,[4] a significant reduction in risk for regular NSAID use that continued into the year before admission (continuing use) was observed, using both cancer controls and controls admitted for trauma and infection, and there was no reduction for discontinued use. In the present analysis of breast cancer, the odds ratio was smaller for discontinued use than for recent use when cancer controls were used, whereas the opposite was the case with noncancer controls. The inconsistencies in the present findings weaken support for a protective effect of NSAID use against breast cancer.

Several potential confounding factors were controlled in our analyses, and estimates adjusted only for age and study center (data not shown) differed little from the adjusted results presented here. Therefore, we believe that our results are relatively unconfounded. It is also unlikely that recall bias affected these results since at the time the data were collected, the study hypothesis was unknown to investigators, interviewers, and subjects.

A few animal studies[11-15] have suggested a protective effect of NSAIDs against mammary cancer, but the animal data is limited. Previous results from epidemiologic studies of NSAID use and breast cancer have been equivocal. Two case-control studies, one population based[7] and one hospital based[6] estimated reductions in risk on the order of 30 to 40%. In the hospital based study, the results varied according to whether cancer or noncancer controls were used: the odds ratio was 0.6 (95% CI 0.4-0.8) for use of NSAIDs at least three times per week for at least five years using noncancer controls, compared to 1.05 (95% CI 0.6-2.0) using cancer controls. It is possible that these results are explained by selective admission of persons with medical conditions commonly associated with NSAID use among the noncancer controls. A 30% reduction in risk (95% CI 4%-50%) was found among women in the NHANES I cohort who

reported taking any aspirin in the month prior to commencement of follow-up.[8] The imprecise definition of aspirin use, lack of information on dose or duration, and the fact that the risk reduction for breast cancer was bigger than that reported in the same data for colorectal cancer (OR = 0.9, 95% CI 0.6-1.15) renders these results unconvincing. Two other cohort studies found no association between aspirin use and breast cancer risk. The large Nurses' Health Study found that the use of two or more aspirins per week was unrelated to breast cancer incidence over 12 years of follow-up.[9] In a cohort of elderly persons, the relative risk for daily aspirin use at entry was 0.96.[10] There was no information on aspirin use after entry, and follow-up was less than seven years.

We conclude that the present findings offer little support for a protective effect of NSAIDs against breast cancer. Previous studies also fail to provide consistent evidence of a protective effect. It seems safe to conclude that NSAID use does not increase the risk of breast cancer. In addition, if there is a protective effect, it is likely to be quite small and perhaps beyond the resolving powers of observational methods.

This report is based on the draft of a manuscript on NSAID use and breast cancer risk. The manuscript will be submitted for publication in the next several months.

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